تسوى حي بولونيا

Histiocytoses

- EMed
- Bolognia
- Darruti

What is Histiocytes ??

they are tissue Macrophages that derived from Blood Monocytes (as) following

BM derived Promonocytes
(Precursor cells)

↓

Blood Monocytes
(half life 71 hr)
then:

↓

Migrate to tissues
to differentiate into
2 Types of
Histiocytes

↙ ↘

Professional Phagocytes (Macrophages)
2 Types
- Immature Macrophages (Inflammatory Macrophages)
- Resident tissue Macrophages.

[Cells that responsive to chemotactic stimuli & are attracted to site of inflamm]

(F) "Ag presenting cells"
↓
Dendritic cells (DC)
- Epidermal
  "LC"
- Dermal:
  ↓
  Dendrocytes

Funct^n

1- phagocytosis
الاهم

2) Ag presentat^n
(via MHC II)
to sensitized
T-Cells only
(not Naieve
nor Memory)

3) Cytokines product^n:
- IL1
- IFN-B
- GMCF

1

Cut. dendritic Cells
(Ag presenting Cells)

Ⓕ < Ag presentat^ (+++)
± phagocytosis
to 3 T Cell Types

Epidermal Langerhan's cells

S100
CD 1a
CD 207

Dermal dendritic Cells

. Dermal dendrocytes

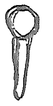
- 2 Types :-
  - ① Type I :-
    - فوق - upper dermal
    - Known Funct^ → Phago-cytosis → . Melanin . Hemosid.
      → Ag pres-ent
    - Factor XIIIa +ve
  - ② Type II :-
    - تحت - lower dermal
    - Unknown funct^
    - CD34 +ve

. site: supra basal (2-8% of Epid. Cells)

. Morphology : - dendritic
- pale Staining Cytoplasm
- Convoluted Nucl
- chic cytoplasmic granules called

مضرب "Birbeck granules"

(tennis Racquet)



. Rod shapped ē Terminal Vesicular dilatat^ [tennis Racquet] → represent Subdomains of endoplasmic recycling Compartment & form at sites where protein Langerin Accomulat^

- only in → LC
  → ± Hairy Cell. leuk. Cells.

→ derived from ! CM by endocytosis.

. Receptors of it :-
. MHC II
. Fc IgG
. C3b
. CD1 (role in Ag presentat^)
. S100.

. Funct^ : Ag presentat^ to T cells → Sensitized
→ Naieve
→ Memory

How?? by (1). Ag endocytosis
(2). Ag Processing (by lyzosomal enz)
(3). reexpressing Ag on surf bound to MHC II → efferent Lymphatics

- **S100**
  - MCs → hyperpigmentation
  - LCs
  - schwann cells.
  - Interdigitating Cells.
  - undetermined cells

- **Factor XIII a**
  - Endothelial → (vascular)
  - Type I dermal dendrocytes. (DF)

- **CD34** :-
  - ⊙ Endothelial (vascular)
  - ⊙ Type II dermal dendrocytes. (DFSP)
  - ⊙ Mast cells
  - ⊙ stem cells.

- **CD45**: Common leukocytes Antigen.

Histiocytosis

Def: reactive or Bg^{mg} Accumulat^ of Histiocytes in Many organs. According the the Type of infiltrating Histiocytes there are 2 Types of Histoicytosis → Langerhans : LCs infilt. → Non Langerhan infilt by C other than LCs

(LCH) Class I: Langerhans' cell histiocytosis (Histiocytosis X)

Non-cancerous ('reactive') increase in number of Langerhans' cells (histiocytes within the epidermis)

· +ve : S100, CD1a, Langerin (CD207) & birbeck gls.

- Letterer-Siwe disease < 2y
- Hand-Schuller-Christian disease 2-6y
- Eosinophilic granuloma 5-15 Skin
- Congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker disease) ← Benc

Class II: Non-Langerhans' cell histiocytosis.

Class IIa: Dermal dendritic cell histiocytosis (DDH)

Non-cancerous ('reactive') increase in number of non-Langerhans' cell histiocytes.

ch^ BY:
- −Ve: S100, CD1a, Birbeck gls.
- +Ve: CD68, Factor XIIIa
- Hist. Xanthogranulomatous react^.

- Dermatofibroma (DF) (+Ve XIII a)
- Juvenile xanthogranuloma (JXG) أطفال
- Benign cephalic histiocytosis (BCH)
- Generalised eruptive histiocytoma
- Papular xanthogranuloma
- Erdheim-Chester disease
- Progressive nodular histiocytosis
- Solitary reticulohistiocytoma (Solitary Retic.)
- Xanthoma disseminatum

Class IIb: Non-Langerhans' cell, non-dermal dendritic cell histiocytosis

Reactive increase in number of (non-Langerhans' and non-dermal dendritic) histioctyes

- CD68 (Macrophage)
- MAC 387 (immature Macrophage)
- HAM56.

- Diffuse plane xanthomatosis
- Reticulohistiocytosis. (+ Grenz zone)
- Necrobiotic xanthogranuloma →
- Rosai-Dorfman disease (S100)
- Familial haemophagocytic lymphohistiocytosis
- Familial sea-blue histiocytosis
- Hereditary progressive mucinous histiocytosis

Class III: Malignant histiocytoses

Cancerous change in histiocytes

- Monocytic leukaemia
- Malignant histiocytosis
- True histiocytic lymphoma

Langerhan's Cell Histiocytosis (Histiocytosis -X)

(LCH)

Def: reactive condition in ω cells with phenotype of Langerhan's cells Accomulate in various tissues causing damage

Etiopathogenesis unknown but ±:-

① **Infect^n** < TB / HSV 6 (Was found in large N° of patients → ++ LC & ↓ Immunological Control of Histiocyte prolif.

② **Immunological** (IL17 → fusion bet Giant cells & LCs).

③ **Malignancy:** LCH cells are clonal cells.

- **General character:-**
  - reactive Conditions d.t infilt by LCs-like Cells called LCH cells
  - all Types are
    - → S100 +ve
    - → CD1a +ve ± CD 207 = langerin
    - → Birbeck grs. (+ve)
  - affect^n ±
    - ① **Single System** e.g → (SS-LCH)
      - الأشهر
      - Skin
      - Bone
    - ② **Multisystem** (MS-LCH)
      - أشهر
      - Skin
      - Bone
      - L.N
      - Liver & Spleen
      - Lung
      - Blood
      - CNS
      - CVS

↓ **definit^n:-** ≥ 2 organs or organ systems.

Prognosis

→ early onset < 2Ys & multisystem affect^n → Poorer prognosis.

- **Risky organs:-**
  - Spleen
  - Liver
  - Lung
  - Blood (BM) (Hematopoietic)

Langerhan's Cell Histiocytosis:-

(Histiocytosis-X (الاسم قديم) → because unknown AE

1- Letterer Siwe dse (Acute disseminated) [LSD]

- Age <2 Ys

الأهم - **Cut** : Crusted, purpuric Papules, Vesicules & pustules at scalp & Grion

→ MM & Nail affect^n^
- gingivitis
- loose teeth
- paronychia
- Dystrophy

An infant with crusted purpuric papules + seborrheic-like eruption in the scalp and groin (E focal) should raise the suspicion of ↓ LCH

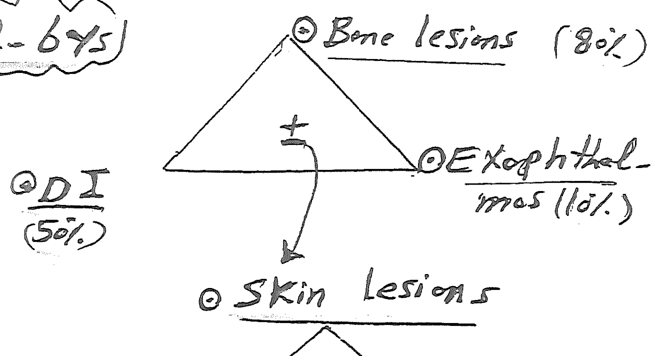
بالترتيب **Systemic** :
- Bone : osteolytic bone lesions
- L.N : Lymphadenopathy
- Lung : Pulm infilt.
- Liver : HSM
- Blood : Anemia & thrombocytopenia

Prognosis:
- → Good (Bg) : if only Bone affect^n^.
- → Bad (Mg) : if early onset, Visceral Affect^n^ (HSM, purpura, thrombocy & Nail affect^n^ (Syst)

2- Hand-schuller christian (HSCD)

(chr. Multifocal)

(2-6 Ys)



Skin lesions
- early: LSD like
- Later: ulcerated plaques at axillae, Mouth & Genitalia

Uncommon : Visceral affect^n^

3- Hashimoto pritzker

(Cong. self Healing Reticulohist

مهم
- birth or Infancy.
- Cut. only : disseminated reddish brown Nods. & plaques → ulcer → Atrophic dsypigm. Scars.

Course: self limiting (8-24 ms) then ± recur or → LSD.

4. Eosinophic granuloma (Bg localized)

(5-15 Ys)

Bone only: osteolytic lesions at Flat bones (Scalp Vault) → ± Fracture

Course : Self limiting or → LSD or HSCD.

Diagnosis of LCH. (3 levels)

1. Histopathology
2. Immunohistochemistry
3. E/M

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1. Histopathology (CLM):

Histopathology of LCH

. in All types: there are LCH Cells ῶ ch By:

ovoid ↓ Large ē irregular vesiculated

- → "Kidney shapped" nucleus (d.t central indentation) or Coffee bean (d.t peripheral ind.)
- Abundant slightly Eosinophilic Cytoplasm.
- Birbeck grs (50%) [by E/M]

In Hashimoto Pritziker:
LCH Cells + multinucleated cell.
- mid & upper Dermis.

. There are 3 Types of Reactions:

- **LSD**
  - ↓ Proliferative Reaction
  - LCH Cells infilt. upper dermis & invade epid. in many areas.
- **Hand-Schuller** (PXQ)
  - ↓ "Xanthomatous React."
  - . upper dermis → Foamy Histiocytes
  - . upper dermis → multinucleated giant Cells
  - EB (++), Touton (±) → multinucleated giant Cells
- **Granulomatous** (Eos. Granuloma ↓)
  - extensive infilt. of LCH Cells ē clusters of → Eosinophils, Giant Cells

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2 Immunohistochemistry:

Both LCs & LCH Cells Show +Ve:
- S100
- CD1a
- CD207 (Langerin)
- Birbeck grs.

. So How to differentiate ??

. CBC
LFTS
BMA
urine osm.
XR MRI → other Inv.

NB on LCH

- **Adult LCH:**
  - rare
  - AbnL presentat: Flexural & perianal ⟨ psoriasiform, vesicular & papulovesicular ⟩ Crusted lesions.

- **Malignant LCH:**

الجديد

A. Langerhans Cell Lymphoma = Langerhans Sarcoma

- Solitary, Lymphoma like Tm
- Poor prognosis
- Path. → atypical dendritic histiocytes.
  $\bar{w}$ are +ve ⟨ S100. Neurone specific Enolase ~.

B. LSD with Malignant outcome:

- Early onset < 2y.
- Visceral involvement
- Purpura & anemia.
- Clonality & Cytological atypia.

LCs	LCH Cells.
· ha~~v~~e dendrites. · Convoluted nucleus · Birbeck grs. (+++) · CD1a + · S100 · CD 207 (Langerin)	· No dendrites (ovoid) · Kidney shapped. · ± birbeck grs (sic) as LCs + · PNA (Peanut agglut.) · PLAP (placental AK. ph.).

· Cause of death: Inf, Systemic affects, Haemo-Phagocytosis.

Treatment of langerhans cell histiocytosis (revise ē 2012) #g skin dis

Single-system disease			Multisystem disease
Skin		Bone	
Children	Adults		
Observation or topical nitrogen mustard	Topical nitrogen mustard ✓ PUVA CO₂ laser Thalidomide Isotretinoin	· Surgery · Glucocorticoid injections · Radiotherapy · Monochemotherapy (in multiple bone lesions)	● Monochemotherapy with vinblastine or etoposide, preceded or not by glucocorticoid administration ● Nonresponders may be treated with polychemotherapy

· DD of LCH

1 LSD:

- SD
- AD

- Wiskot Alderich
- Darier
- Hashimoto Pritzker

- Sinus Histiocytosis
- Hemophagocytic Syndrome.

2 HSCD

- Xanthoma disseminatum
- JXG.

Non Langerhans Cell Histiocytosis

Class IIa- Dermal dendritic Cell Hist.

- Juvenile Xanthogranuloma
- papular Xanthoma
- Xanthoma Disseminatum.
- Benign Cephalic Histiocytosis (BCH)
- Generalized Eruptive Histiocytoma (GEH)
- progressive Nodular Histiocytosis
- Reticulohistiocytosis (Solitary type)
- Others
  - Erdheim
  - Dermatofibroma.

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(7) ملخص

- مترحين
  - JXG
  - BCH

  EM: Coma Bodies (Both) JXG: Foamy Giant Cells; BCH → No.

  Reticulo Histiocyt

- 2
  - Generalized eruptive Histiocytoma
  - progressive Nodular Histiocytosis (or am

- Xanthoma:
  - Papular
  - disseminatum

- Reticulo Histiocytoma. (Giant Cell Retic.)

إهتمام

Juvenile Xanthogranuloma (JXG)

(Nevoxanthoendothelioma)

- The most Common Type of Histiocytosis (of all)
- Age
  - 90% Childhood → M > F
  - 10% Adulthood → M = F (So the term Juvenile is not Accurate).
- it may affect: Cut. / Extracut.
  - Skin.
  - MM (rare) → ulcerating Nodules at lat. tongue & palate
  - Eye
  - Lung
  - Liver
  - CNS
  - CVS
  - Testes.
  - Associations

أشهر Systemic organs بالترتيب ← Eye, Lung, Liver

- Cut. Manifestations: (80 – 90%) appear in the First year & usually Solitary lesions
  - 1 lesion
  - 1st y
- lesion: Dome-shapped, reddish-brown or Yellow Nodule usually affects the head & Neck (also ± upper trunk & extremities) $\xrightarrow{\text{fate}}$
  - Childhood $\xrightarrow[\text{Y}]{3-6}$ resolve c̄ scar, pigm.
  - Adult: → more persistent
- According to size of lesion it may be Classified as:
  - Micronodular (papular): < 1 Cm & Multiple (<1Cm) [illegible]
  - Macronodular: > 1 Cm, single or few (1–2 Cm) (>1 Cm)
  - Giant: > 2 cm.

- Adult JXG Ch By:
  - Solitary
  - persistent.

Crynoform Sign: JXG affect the Nose → diffuse enlargement.

- Clinical Varieties: in site / in lesion ↗
  - in site: Lips, Toe, Scrotum.
  - Lichenoid
  - Keratotic
  - Pedunculated
  - Clustered
  - S.C
  - plaque
  - Crynoform

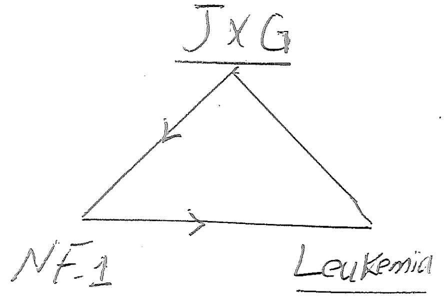
- **Visceral Manifestations**: the most Common affected organs are: بالترتيب

Eye is the most Common extracut. organ affected

- Eye (< 1%): Iris affect. $\xrightarrow[\text{HOC}]{\text{Ant Chamber}}$ glaucoma & Hyphema → Blindness.
- Lung
- Liver
- CNS
- CVS

Liver, CNS → Cause of death (± Spont. Resolut.)

- Testes
- Triple Association:



CALM
.20 % ass.
.30% Leukem

NB: . JXG ass. ē CALM in ≃ 20% $\xrightarrow[\text{risk}]{\uparrow 30}$

لو شفت دا حاجا ؟؟

. JXG + NF1 $\xrightarrow[\uparrow\uparrow\text{ risk of}]{\text{30 times}}$ Leukemia. (Chr. Myelogenous)

- **Diagnosis** (3 levels)

أهم حاجة Coma bodies

- **Histopathology** (upper dermal SC)

(Xanthogranulomatous)

- Foamy Cells (Histiocytes)
- Touton Giant Cells
- ± inflamm. Cells
- Fibrosis (late)

- **Immunohistochemical** (Dermal Dendrocytes)

- +ve: CD68, XIIIa (13a), HAM56
- −ve: CD1a, langerin (CD207), S100

عكس ترتيب

- **E/M**

Histiocytes CF BY.

① **Nucleus**: irregular vesicular ē Pseudo pauds

② **Cytoplasm**

Coma shapped bodies

بيرتبط

بيربك

Birbeck.

Treatment (Not needed as it is self limiting).

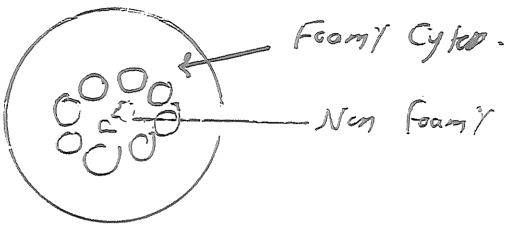
- **Excision** → For cosmetic reasons.
- **Ocular lesion.** → Topical Cs.
- **Systemic lesions** →
  - Cs + Cyclosporine
  - Chemotherapy

NB . **Touton Giant Cell,**

أكليل زهر. Wreathy arrangement of Nuclei (ring) around ~~Non~~ foamy cytoplasm (in center) & Foamy Cytop. outside The Nuclei.

- **Center**: non foamy
- **rim**: foamy.

→ تعى



• Papular Xanthoma

- Generalized, yellowish, asymptomatic "small papular" skin lesions on [illegible] & head.

In adults MM is affected.

- **NO** →
  - Coalescence of lesions.
  - Lipid Impairment
  - Visceral involvement ✓
  - **D.I.**
- **Pathology**: Foamy (Xanthomatized) Histiocytes + Touton Giant Cells.

[NO Inflamm. cells]

- **Fate** <
  - **Children**: spont. resolution at (1-5Y.) → anetoderma like
  - **Adults**: Persist.

Xanthoma Disseminatum

(Montgomry synd.)

. usually Male < 25 Y. (but any age 8m.-80 Y.)

. Triad of : 1. Skin lesions

2. MM lesions (50%) at

- Orophar/nx → dysphagia
- Larynx → dysphonia & obst
- Conjunctiva & Corneal → ± Blindness.

3. D.I (40%)

↳ d.t hypothalamic & pituitary stalk affect. . mild & Transient.

Face
. Flexures
. MM
. D.I
→ ē Coalescence

. Skin lesions: hundrends of Bilat., symmetrical yellow or reddish-brown Papules & Plaques كتير on Flexures, Face & Eye-Lid → ω̄ ± Coalesce → Verrucous.

. Course: may → Resolve / persistent / progressive. [good prognosis except for Laryngeal Lesions]

. NB: it may be ass. ē MM; Here it will be presented by "Sclerotic Variant": Extensive Keloid like at Trunk, Abd. & limbs.

. HP: dermal Infilt. ē Spindle Histiocytes, Foamy Histiocytes, Touton Cells & other Inflamm. Cells.

. Ht:
1. Air-way $\xrightarrow{obst.}$ Radioth.
2. Clofibrate & Cyclophosphamide [illegible]
3. Excision, Cryo, IL & dermabrasion.

ثبوحي وبولونيا

Histiocytoses

- EMed
- Bologna
- Darouti

- what is Histiocytes: ??

  - they are tissue macrophages that: derived from Blood Monocytes @ following

BM derived promonocytes
(precursor cells)

↓

Blood Monocytes
(half life 71 hr)
then:

↓

Migrate to tissues to differentiate into 2 Types of Histiocytes

↙ ↘

Professional Phagocytes (Macrophages)
2 Types:
- Immature Macrophages (Inflammatory Macrophages)
- Resident Tissue Macrophages.

Funct^n:
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3. Cytokines product^n:
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   - IFN-β
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[cells that responsive to chemotactic stimuli & are attracted to site of inflamm.]

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Dendritic cells (DC)
- Epidermal "LC"
- Dermal: ↓ Dendrocytes

Cut. dendritic Cells
(Ag presenting Cells)

(F) < Ag Presentat^ (+++)
± Phagocytosis
→ To 3 T Cell Types <.

Epidermal Langerhans Cells

- Site: Suprabasal (2-8% of Epid. Cells)
- Morphology:
  - dendritic
  - pale Staining Cytop.
  - Convoluted Nucl.
  - chic Cytoplasmic granules Called

"Birbeck granules"

- Rod shapped ē Terminal Vesicular dilatat^ [tennis Racquet]

→ represent Subdomains of endoplasmic recycling Compartment & Form at Sites where Protein Langerin Accumulat.

- only in < LC
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Dermal dendritic Cells

- Dermal dendrocytes

- 2 Types:
  1. Type I:
     - upper dermal
     - Known Funct^ < Phagocytosis (→ Melanin, Hemosid.), Ag presentat
     - Factor VIIIa +ve
  2. Type II
     - lower dermal
     - Unknown Funct^
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- **S100**
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  - LCs
  - Schwann Cells.
  - Interdigitating Cells.
  - undetermined Cells.

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Class II: Non-Langerhans' cell histiocytosis.

Class IIa: Dermal dendritic cell histiocytosis

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. Hist. xanthogranulomatous react^.

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- Juvenile xanthogranuloma ✓(JXG)
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- Generalised eruptive histiocytoma ✓
- Papular xanthogranuloma
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- Solitary reticulohistiocytoma (Solitary Retic.)
- Xanthoma disseminatum ✓

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Reactive increase in number of (non-Langerhans' and non-dermal dendritic) histioctyes

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. MAC 387 (immature Macrophage)
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- Reticulohistiocytosis. (+ Grenz zone)
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Cancerous change in histiocytes

- Monocytic leukaemia
- Malignant histiocytosis
- True histiocytic lymphoma

Langerhans Cell Histiocytosis (LCH)

(Histiocytosis X)

Def. reactive condition in ω cells (with) phenotype of Langerhans cells Accumulate in (various) tissues causing damage.

Etiopathogenesis unknown but ±:

① Infect⁻ < TB / HSV 6 (was found in large No of patients → ++ LC & ↓ Immunological Control of Histiocyte prolif.

② Immunological (IL17 → Fusion bet Giant Cells & LCs).

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- General character:
  - reactive Conditions d.t infilt. by (LCs-like) Cells called LCH Cells
  - all Types are < S100 +ve / CD1a +ve & CD207 / Birbeck grs. (+ve)
  - affect⁻ ±

(SS-LCH) ← Single System e.g
[. Skin
[. Bone

Multisystem (MS-LCH)
أهم (٣) [. Skin
[. Bone
[. L-N
. Liver & Spleen
. Lung
. Blood
. CNS

↓ definit⁻: ≥ 2 organs or organ systems.

. Prognosis:
early onset <2y & multisystem affect⁻ → Poorer prognosis.

. Risky organs
[. Spleen
[. Liver
[. Lung

. Blood (BM) (Hematopoietic)

Langerhans Cell Histiocytosis:

(Histiocytosis - X (الاسم قديم))

1. Litterer Siwe (Acute disseminated) [LSD]

- Age < 2 ys

الأهم
- Cut. : Crusted, purpuric Papules, vesicles & pustules at scalp & Grion
  - MM & Nail affecti
    - ↓ gengivitis
    - . loose teeth
    - . Paronychia
    - . Dystrophy

> An infant with
> crusted purpuric papules
> +
> seborrheic-like eruption in the
> scalp and groin (ē fever)
> should raise the suspicion of
> ↓
> LCH

- Systemic :
  - . Bone : osteolytic bone lesions
  - . L.N : Lymphadenopathy
  - . Lung : pulm infilt.
  - . Liver : HSM
  - . Blood : Anemia & thrombocytopenia

- Prognosis
  - Good (Bg) : if only Bone affecti.
  - Bad (Mg) : if early onset, visceral Affecti (HSM, purpura, thrombcy.) & Nail affecti

---

2. Hand-schuller Christian (HSCD)

(Chr. Multifocal)

(2-6 Ys)

- Bone lesions (80%)
- Exophthalmus (10%)
- DI (50%)
- ±
  - ↓ Skin lesions
    - early : LSD like
    - Later : ulcerated plaques at axillae, mouth & Genitalia

- uncommon : visceral affecti

[illegible]

3. Hashimoto Pritzker

(Cong. Self Healing) ([illegible])

- birth or Infancy.
- Cut. only : disseminated reddish brown Nods. & plaques $\xrightarrow{\text{ulcer}}$ Atrophic dyspigm. Scars.

- Course : self limiting (8-24 ms) then ± recur or → LSD.

4. Eosinophic granuloma (Bg localized)

- 5-15 Ys.
- Bone only : osteolytic lesions at Flat bones (Scalp Vault) → ± Fracture.
- Course : Self limiting or → LSD or HSCD.

Benign Cephalic Histocytosis

(BCH).

- 2-12m
- 2-8Ys
- No — MM / Visceral / Ht / Touton or giant cell

. onset: 2-12 ms ⟶ resolve at: 2-8 Ys.

. C/P: yellowish-red flat macules & papules at Face & Neck (± → chest & trunk) ⟶ more flattening & Hyperpigm ⟶ resolve spont at (2-8 Ys) but may leave Hyperpigm.

. No < MM or / Visceral affect⌒ (case report DI). / ~~Ht~~

. Diagnosis: Histiocytes rich in comma shapped Bodies (No touton nor Giant Cells)

Comma Shapped Bodies ↓
- JXG
- BCH

. Ht: Self-limiting.

---

(1) . **Progressive Nodular:**
- Any age
- Papules & Nodules (sp. at Face) ↓ leonine
- persistent
- ± MM

(±) ↙ ↘ . Leonine . MM

(2) **Generalized Eruptive Histio.**
- Adults.
- papules only ± "dark blue" (غامق)
- resolve spont. ± e — dyspigm. / Scar.

(3) **Papular Xanthoma**

[illegible]

(HP)

(1) **Prog. Nodular:** (No effective Ht)
- Early: Foamy & scalloped Histiocytes.
- Late: Spindle shaped arranged in storiform pattern.
- occasional Giant Cells.

25

(2) **Generalized Eruptive:**
- Neither Foamy Nor Giant Cells.

لما تكون حالة ...

Eruptive Syringoma

((DD))

(1) Eruptive syringoma.
(2) Eruptive Xanthoma
(3) Papular "
(4) Progressive Nodular Histiocyt.
(5) Generalized Eruptive Histiocy.
(6) disseminated variant of BCH.
(7) Mastocytosis.

* No foamy Nor Giant Cells:
- BCH
- Generalized Eruptive.

Class II b Histiocytosis

(Non LCs, Non dermal dendritic Histiocytosis)

- Reticulohistiocytosis
- Necrobiotic XG
- Diffuse plane Xanthoma
- Sinus Histiocytosis ē Massive L.N
- Indeterminate Cell Histiocytosis.
- Familial hemophagocytic Lymphohistiocytosis
- Familial sea blue histiocytosis
- Hereditary Progressive Mucinous Histiocytosis
  (Hist. with Mucinosis)
- Histiocytosis with Necrosis
- Indeterminate cell Histiocytosis.

نعم: الاهم

- Multi Centric
- 2 Xanthomas
  - NBXG
  - Plane Xanth. (Normolipemic)
- Sinus Histiocytosis.
- malakoplakia

Reticulohistiocytosis

(3)

Solitary | MultiCentric | Cong. Self. Healing (Hashimoto - Pritzker).

- M = F
- Young adults.
- Class IIa

- F > M
- 4th decade
- Class IIb.

---

① Solitary Reticulohistiocytoma :

XG اللي بيكبر
DF [illegible]
في (2) Head++.
> شكل

- usually, single, < 1cm, yellow-red Nodule on head ⟶ resolve spont.
- rarely: Multiple without systemic affect.

---

② MultiCentric RH: ⟶ Pentad + Associations..

(lipoid dermatoarthritis) (⑤: Skin, Joint, MM, Mg, Hyperlipid)

1. Skin lesions (90%): Skin colored - red or brown Nodules & Papules Mainly Acral.

   ① Juxta-articular, in proximity of affected Joints, dorsal Hands, Feet, extensor elbows

   ② Face & scalp: ear pinna (chic)
   ± Leonine face

   ③ Nails: periungual chic "Coral bead" & Nail dysatrophy.

(3:1)
- F > M
- 4th decade.

2. MM
- oral, Nasal, pharyngeal & ocular.

٥٠٪ قبل الجلد

3. Polyarthritis
- Symmetric, Erosive & Mutilating.
- Typically: affects Hands.

- Spontaneous Resolution ± occur in 5-10ys.

(مهم جداً)
Subtle form: Flat macules & papules of dorsal hands: Very Similar to DM

تذكر:
Coral bead
Ear pinna
Pentad -

4. Mg (30) — Stomach, Bronchogenic, Cervical.

5. Hyperlipidemia (30%)

Associations

- Autoimmunity
- Systemic vasculitis

- +ve tuberculin test
- ↑ ESR, IgG, fever, ↓ wt.
- heart, Eye, Lung, GIT lesions

DD of Juxta-articular Nodules
- MCRH
- R.A
- Sarcoidosis
- Xanthomatosis
- Gout

. Histopathology: oncocytic Histiocytes + Giant Cells + Others:

↑ mitochond → acidophilia of cytoplasm

Histopathology → skin, Synovial Biopsy.

oncocytic Histiocytes (ē Pink / oncocytic cytoplasm)
- Contain lipid
- +ve PAS.

Others:
- Lymphocytes
- Eos.
- Plasma Cells
- Fibrosis (old lesions)

Giant Cells → Cytoplasm / Nuclei

. Cytoplasm (very!)
- Ground. glass (Homogenous = Non Foamy) &
- Eosinophilic.

Nuclei
- 1-12
- arranged — Central, peripheral or Haphazard

- GrenZ Zone is +ve

. Immunohist:
- +ve Histiocytes of — ATPase. / lysozymes / α_1 Antitrypsin
- Classical Monocyte / Macrophage Markers are +ve: CD 68, HAM56 & Mac 387
- factor XIIIa < +ve in Solitary. / −ve in Multicentric.

. Treatment
- CS + AZathioprine
- CycloPhosphamide & CYA
- Recently: Alendronate / Anti-TNF α

- Necrobiotic Xanthogranuloma → See granulomas
- Diffuse plane Xanthoma → " Xanthomas.

• Sinus Histiocytosis with Massive L.N (Rosai-Dorfman dis).

الاسم الأفضل عشانه بعمل ٧٤ =
(extranodal)

- usually affect children & Young adults. (10-30)
- Course: indolent, self limited ē protracted course marked by remission & Exacerbat̄ .

C/P = Nodal affect̄ + Extranodal affect̄ + Association.

- 90%
- Massive, bilat., painless Cervical L.N (Chic)

Extranodal affect̄:

- 40%
- Commonest is the skin 10%.
- Skin affect̄ ± the only finding ēout L.N (Cut. Sinus Histiocytosis)
- C/P: red-brown, Xanthomatous Macules, Papules, Nodules usually at < Eye lid / Malar area.

Association:

- Fever
- ↑ ESR
- ↑ IgG (Hypergamma),
- ↑ Neut.
- "Immune dysfunct̄" (١٥) = [15%]
  → usually: anti-RBCs antibodies & Joint dis.

So Rosai-Dorfman Synd. ±:
- Nodal (from interdigitating Histiocytes)
- Cutaneous.

Bad prognostic signs:

1. Autoimmunity.
2. disseminated Nodal dis.
3. Visceral aff.: renal or Lower RT involvement, Hepatic

(ادابيوس) - **Prognosis**:
- 60% → persist
- 20% → resolute
- 10% → die.

Diagnosis

"Lymphophagocytosis"

Pathology
Biopsy
Nodal — extra-Nodal

Histiocytes + inflamm. cells + Emperipolesis

Histiocytes:
- Cytop.: foamy
- Eos., Abundant
- Nucleus: large vesicular
- Feathy border

inflamm. cells:
- Lymphocytes
- plasma cells.

Emperipolesis (chic but not unique).
→ (phagocytosis of intact lymphocytes & plasma cells by Histiocytes)

infiltrating Sinuses of L.N or dermis of skin.

Immunohistochemical
- CD68, HAM 56 & Mac 387 (+ve)
- +ve S100
- CD1a −ve

- DD → diseases ē Massive L.N:
  - Lymphomas (H. & non H.)
  - CLL.
  - Metastases.
  - infectious L.N
  - Kikuchi's dis: ?? [Histiocytic Necrotizing Lymphadenitis]
    - C/P: Fever + Tender Cervical L.N
    - asian, young women.
    - Normal: WBCs, ESR & HcT.
    - Path: LN shows
      - Necrotic foci
      - Cellular population of large blastic lymphocytes & Histiocytes.

[illegible] Histiocytes engulfing Apoptotic...

Ttt of Rosai-Dorfman

- No Ttt (self-limiting)
- Indications: destructive, disseminated dis, physical compromisal
- Types:
  - surgical
  - radio
  - Cs
  - Alkylating Agents → Vincristin, Vinblastin.

✓ thalidomide (±)

Indeterminate Cell Histiocytosis

(LCH & non LCH بيجمع خصائص بين)

- Children & Adults.
- Self limiting
- CIP
  - Generalized : GEH like
  - Solitary : single, soft, Erythem. lesions
  - Ulcerat ± occur.
- rare : ocular & visceral affect
- Path: as LCH (Vacuolated / Xanthomatised Histiocytes throughout ! dermis)
- شرط أساسي. → Immunohist
  - +ve CD1a, S100
  - +ve CD68, HAM 56 & Mac 387.
  - -ve birbeck granules
- tt (not required as it self limited)

(±) · PUVA
· Chlorodeoxyadenosine.

[illegible] • Familial – hemophagocytic lymphohistiocytosis

- AR
- death ē in 12 ms
- wide spread infilt. of many organs by Lymphocytes & histiocytes showing prominent "Cytophagocytosis".
- C/P
  - Fever
  - URTI
  - UGITI.
  - Immunological abnormalities
  - Non Specific Maculopapular rash.
  - hyper cytokinemia: ↑ IFNγ - TNF-α, IL 6
- TH BM & Hemopoietic Stem Cell transplantation.

• Sea Blue Histiocytosis : Inherited : rare skin / Acquired : pigm. c nod.

- ± Familial inherited or Acquired.
- Clinically: histiocytic cell contain cytoplasmic granules that stain (blue-green) ē (Azure) Geimsa & blue with May-Gruenwald stain
- these Histiocytes infilt. systemic organs & ! skin. →
  - Papules
  - Eye lid swelling
  - Patchy gray Pigm. of face & trunk.

Inherited Type ± ass. ē : Neurological abnormal.

Malakoplakia

- rare Immunodeficiency dis. of Macrophages. ↑ d.t Abnl immune response to E. Coli
- usually affect Urinary Bladder & ± other sites < GIT / Skin
- Cut. affection is rare: perianal & perigenital Papules, Nodules, plaques & Tms ; Pink- Yellow ± ē Central dimple or sinus
- HP: Hansmann Histiocytes: Histiocytes ē chic Michalis-Guttmann Bodies (Stain +ve For < Ca+ / Iron & when fully developed → like owel's eye).

TH
- Surgical → then Anbiotic (Septrin)
- Vit C
- Clofazemine.

• Hereditary progressive Mucinous Histiocytosis
(Histiocytosis with Mucinosis)

- AD.
- Start in Childhood (1st decade) & ↑ ē Age
- Skin Colored _ red brown Nodules that affect
  - Nose,
  - Hand,
  - Forearms,
  - thigh.
- Path: . Epitheloid & Spindle Shapped Histiocytes
  - Mucin deposit^{n} (by Alcian or Toludin Blue).
- No
  - Systemic affect^{n}
  - spont. resolut^{n}
  - H.

- Histiocytosis ē Necrosis = "Kikuchi dis" (see DD of sinus Histiocytosis) -

---

• Erdheim- Chester dis: (rare)

- Any age
- Cut Manifs: Yellow nodules & indurated Plaques at Perorbital, Trunk, scalp & Extremities.
- Systemic Manifs:
  - DI
  - Bony lesions (Bone ache of legs)
  - Exophthalmos.
  - CNS, lung, adrenal, renal & testes.
- death >50%

تقسیم‌بندی بولونیا

Bg. Melanocytic Neoplasms

تقسیم بولونیا
جدول
pigm. صفحه ۳

- Freckles (Ephelides) ← → See pigmentary
- Lentigenes ←
- CALM ←
- Becker's Nevus ←
- Halo "
- Nevus Sp.lus
- Dermal Melanocytosis
- Cong. Melanocytic Nevus
- Acquired Melanocytic Nevi
- Spitz Nevus
- Atypical (Dysplastic) Nevus

Others:

- Melanocytic Nevi of genital & Flexural skin
- Melanocytic Nevus of Acral skin.
- Recurrent Melanocytic Nevus (Pseudo-Melanoma)
- Pigmented Spindle Cell Nevus.

Melanocytic Nevi قراني

2017

وحمة - شامة (**Moles**)

- **Def**: Bg Neoplasms or Hamartomas Composed of Type of MCs called Nevus Cells

2 Main differences bet it. & NL MCs:

① present in Nests (NL MCs present singly)

②. Has No dendrites (Except in Blue Nevi).

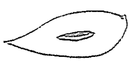
③ Doesn't deliver Melanin to surrounding KCs.

Nevus Cells Has 3 Types (ELN)

- **Type A** (Epitheliod like)
  - in lower epid & upper dermis
  - Epitheliod like (tall or large simulating epid. KCs)
  - Contain Considerable amount of Melanin.

- **Type B** (Lymphocytoid)
  - Mid dermis
  - Lymphoid like (small lymphocytes)
  - Very little or No Melanin.

- **Type C** (Neuroid)
  - Lower dermis
  - Neuroid lik (Schwann Ce like) ~~or~~ fibroblast like):
  - Elongated ē spindle nucleus



  - **Rare** Melani

- Origin (Embryology) either:

①. **Dual origin** Nevus Cells of < upper dermis originate from MCs / lower " : Schwann Cells

② **Single origin**: from Neural Crest ū gives < Nevoblast → Nevus Cells / Melanor → Leptomeninges, Uvea Tract, Derm & HF / Schwann Cell

(NAevus انكليزي
Nevus امريكي)

Classificat~ of Melanocytic Nevi

(ONN2)

1. ACC. to ! Age of onset: Congenital / Acquired
2. Histopathological: Junctional, Dermal, Compound & Combined
   [illegible]
3. Atypical & Typical.

---

1 Classificat~ of Melanocytic Nevi acc. to ! Age of onset

- Congenital (<2 ys)
  - True Congenital: appears at birth
  - Congenital like or Tardive Nevi (develop ēin 2 ys after birth)

- Types: (According to Size) (2013)
  - Small <1.5 cm diameter
  - Medium: 1.5-10 cm
  - Large: 10-20 cm
  - Giant: >20 cm
  - Satellite

  - Larger
  - Elevated
  - Dark
  - ± Hair.

- HP Types: Compound

- Acquired (>2 ys)
  - Not at birth
  - usually: start at childhood or early adulthood (1st 3 decades).

- Clinical Types:
  1. Junctional: بقعة غامقة
  2. Compound, بارزة وغامقة
  3. Intradermal: بارزة جداً وفاتحة جداً (Skin Color) وفيها شعر

- HP: Junctional, Compound & Dermal

Difference bet Cong. & Acquired Nevi by HP

- Cong. Nevi ch̄ BY: Nesting of Nevus Cells:
  - Extend deeply to deep dermis & S.C.T
  - clusters around Adnexae & BVs
  - infilt. bet Collagen bundles.
  - Nevus-cell poor Subepid. Zone

Cong. Nevi
- Cong. Melanocytic N.
- Spilus Nevus
- CALM
- Ota.

وطي شي بنزل كتير
لكن لازم تعرفه كلينيكال

Aquired Nevi

C.I.P

1. Junctional Nevus

- Junctional prolif. of Nevus Cell at DEJ
- Clinically: Just Macular Pigmentat^ (No elevat^)
- Nevus Cells are: Epithelioid like

ستذكر كلمة
Nevus عم Cells.

2. Compound Nevus

- Nevus Cells proliferat both at DEJ. & at dermis (upper)
- Nevus Cells are Lymphocytoid like
- Slightly elevated (Papule) Darkly Pigmented.

3. Dermal Neve

- Nevus Cells proliferat at Dermis (No. Junctional Activ
- Nevus Cells are Neuroid like.
- Markedly elevated papule / Nodu ē light or NO Pi

لونها فاتح أو غير مصبغ → ē light or NO Pi

- The Nevus may start Junctional $\xrightarrow[\text{مع الوقت}]{\text{تتحول لـ}}$ Compound or Intradermal So Elevat^ is not a sign of Mg. Malignant Transformat^ in Cong. > Acq.

Congenital Melanocytic Nevi (CMN)

- Types according to size: small < 1.5 cm diameter, Medium: 1.5-10 cm, Large: 11-20 cm & Giant > 20 cm.
- Giant Cong. Melanocytic Nevus: ((Bathing Trunk))
  - 5% → Incid of MM (Compared to < 1% in other Types)
  - 10% → ass. ē Neurocut. Melanocytosis specially if → large, / Axial / Ass. ē Satellit
  - 80% → ± ass ē Satellites.

بنشوفه كتير

Neurocut. Melanosis (NCM)

- Def. either → Cong. Bathing Trunk (Giant N.) or ≥3 Small. Medium Sized "Lesions" (Satellites)

+ Meningeal Melanosis = Neurocut. Melanosis

- Symptomatic → ↑ ICT
- Asympt. (most cases) By MRI

* Complicat^

1. disfigurement
2. Mg
4. dryness & itching: ↓ seb. & Sweat glo.

- Ht of Cong. Melanocytic Nevi: Surgery; or other times (Laser, shave) are ass. with Recurrence

[illegible] . Halo Nevus

(Sutton's Nevus = Perinevoid Vitiligo = leukoderma Acquisitum Centrifugum) (LAC)

- **Epidemiology:**

. Age usually < 20y (usually acquired)

. Associat. → Common: Vitiligo (20%) & other halo nevi (25-50%)
  lesser: atypical Nevus & Melanoma.

. Course → Halo: occurs over period of ws - ms.
  Nevus: → occasionally persist → then (repigmentation of Halo)
  → More likely involute (ws - ms) → (persistance of Halo) for ms - ys (or may ↓↓)

theory of development of the Halo

2 theories:

① Immune response against antigenically altered Nevus Cells ass. ē Tm progression:

[illegible]

هذه نظرية [illegible] إن المصاحب لـ
Atypical Nevus $\xrightarrow{so}$ Immunologic response ass. ē Tumorigenesis

(~ Now favored)

② CMI & HI against non specifically altered Nevomelanocytes & possible cross reactivity ē distant Nevomelanocy

[illegible] ظهور Multiple Halo Nevi

C/P . * Nevus: . Typical brown or dark, flat or raised ē surface scaling or crusting.

~ its Acquired Melanocytic Nevi ~

. Typical Mean
. A - 3 - 6 mm (largest diameter)
. B - regular well defined border
. C - Homogenous color.
. D - Symmetrical

* **Halo**: start as erythema → Hypo or depigm. (May be Examined ē WL) [Symmetrical in Width].

Types of Halo Nevus

1. Inflammatory
   - +ve infilt. by HP
   - هاتشفها لواحدها
2. Non - Inflammatory:
   - -ve Infilt.
   - مش هاتشف
3. Halo Nevus without Halo
   - +ve infilt.
   - clinically: No Halo.

vnZ)

Halo.dermatitis ~~or~~ ECZ
= Myerson's Nevus

- Nevus Surr. by ECZ. may occur alone r ass. ē Halo Nevus
ممكن شيء يتعرض للعضو ادوي

Typical Cs ممكن نقط.
لاتختفى بعد زوالها.
كا يحدث ē Halo nev.

- DD
  - Halo Dermatitis (ECZ.)
  - Halo depigm.:

Melanocytic proliferat ē Halo
- By
  - Atypical
  - MM
  - Blue
  - Spitz.

- Cong. Nevi
- Atypical Nevi
- blue Nevi
- Spitz Nev.
- Melanoma & Melanoma Metastates. (Asymm. Halo)

Non Melanocytic lesions ē Halo
- DF
- SK
- plane warts
- Molluscum
- BCC.
- L.P.
- Psoriasis.
- Sarcoidosis.

Treatment

- All Cases look for
  1. other Halo nevi (25%-50%)
  2. Vitiligo (20%)
  3. Atypical Nevi
  4. Melanoma (or History < Personal / FH)

then if Nevus
- Typical → هانتابعه بس كل فترة
- Atypi → Histo Path

- Any pt > 40 Ys ⓒ "Multiple" Halo nev. → examine for Melanoma (ocular Ma

أساسي **Dermal Melanocytosis** (Dermal Melanocytic Nevus
Ceruloderma)

Pathophysiology

↓

. due to arrest of ~~MCs~~ Migration ~~from on~~ dermis to epid → dendritic & Fusiform MCs.

. due to optical effect (Tyndall phenom.)
→ رمادي Slate-brown or blue-black or
Ceruloderma

. Types: احفظها

1. Mongolian Spots.
2. Nevus of Ota

3. Nevus of Ito
4. Blue Nevus.

---

① Mongolian Spot

. onset: < at birth or 1st week, rarely Childhood → غالبا regress in childhood.

, Etiopathogenesis . MCs reach dermis at 10th w
then either < Migrate to epid. or die
Except at < Scalp
extensor distal extremities.
Sacral area.
↙ أسئلتهن ليه

. why appears blue ?? Tyndall phenomenon
or Slate-brown
(Ceruloderma)

(Slate اللون الرمادي)
للأردواز الحجري -

Def. ↓ reflectance in longer wave length region compared ē the surrounding skin

- longer wave-lengths as: red, orange, yellow
- shorter " " as: blue & violet → reflected

C/P? Most Common sites:

- Sarococcygeal
- Lumbar
- buttocks
- back

] extra sacral variant (Aberrant variant) → Most persistent.

(NB) . Extensive lesions $\xrightarrow[2]{\text{غ}}$ Phakomatosis Pigmento vascularis Types II & IV

. Treatment

1. Reassurance; self limiting
2. Laser

. Nevus of Ota (Oculodermal Melanocytosis

- At birth (50%) or Acquired (around puberty)
- 80% are females
- May affect
  - Skin: at distrib. of Trigeminal Nerve brs (Facial)
  - Eye: sclera → iris mamillo[illegible] (but no visual affect.) or Glaucoma
  - MM: Nasal Mucosa.

#
↓
Q. switched Laser

اول ما تشوف حالة : → Take Care of Eye as:
(سيبك من الجلد وركز في العين)

- Glaucoma
- Melanoma (Most melanoma are ocular)

- Bilateral Variant is called Nevus of "Hori":

لتمييزه عن : unilat. Nevus of Ota

- ♀ 20-70%.
- at Zygoma
- No ocular or Nasal affect.
- ± mis diagnosed as Melasma

. Nevus of Ito

as Ota Nevus but differs in its distribut. at ⟨ shoulder & upper arms
ē distrib. of post. supraclavicular & lat. brachial cut.

Blue Nevus (& its variants)

- **onset:** Acquired (Childhood or adolescence) → rarely Congenital.
- **Etiopathogenesis:** عدم حدوث ارتحال لـ MCs من الـ Dermis
  لـ Epid في منتصف الشهر من عمر الجنين
  في الـ ٣ اماكن دي ← Sites of
  Blue Nevi.

- **Types:** ① "ordinary" ↓ Common Blue Nevi: (0.5-1cm.)
  - Blue or Blue-black papule < 1 cm usually at dorsal Hands & feet (± Face & Scalp)
  - path: NL MCs singly or in Nests in Dermis & Periappendageal.

  ② Cellular Blue Nevi: [May → MM]
  - Nodule or plaque ≥ 1-3 Cm.
  - Buttocks, Scalp > Extremities & Face.

  ③ Mg Blue Nevi [Cut. Melanoma arising (in) or having Features of Blue Nevus].
  - Cut. Melanoma arise on Top of any Blue Nevus or develops de novo
  - Large, Multilobulated plaque at Scalp.

- **DD:** Conditions simulating Blue Nevi: Traumatic tattoo, Compound Nevus, DF, Venous lake, Pigmented BC

Treatment:

1. if: < 1 cm, stable ē No Features of Mg & in Typical sites → No Rx
2. if: large, progressive, multinodular or plaque → Excision. (?? Melanoma)

(2012)

Spitz Nevus

لا تستعمل عشان Melanoma

(Epithelioid & Spindle Cell Nevus / Benign Juvenile Melanoma)

- Def: Type of Compound Bg Nevi affects children & resembles Malignant Melanoma both < Clinically & Pathologically

- Etiopath: May develop denovo or on Top of existing Melanocytic Nevus.

- Epidemiology:
  - Age: 50% < 10 Ys & 70% → 2nd decade (عز الشباب)
  - Sex: M = F.
  - Race: fair skin.

- C/P: - Single, dome-shaped red or pigmented Papule or Nodule usually on legs & Face (in adult → any site)
  (d.t excess vascularity ē minor pigm)
  - the lesion: shows rapid initial growth (1 cm ē in 6ms) then → static For Years but often disapear Spontane

---

- Clinical Varieties
  1. The lesion I:
     - Polypoid.
     - Crusted.
     - Telangiect.
  2. Multiple:
     - Agminated = grouped
     - Disseminated
  3. Atypical
  4. Mg = Spitzoid Melanoma.

- tt: Surgical Excision.

HP

Epi: Nests of Epithelioid & Spindle cell shaped MCs
- arranged in clusters ē Giant Multinucleated Nevus cells among them.
- ē Vertical Fascicular (bundles) arrangement.

+

- Kamino Bodies: Eosinophilic, PAS +ve Globules Among Nests (degenerated KCs)

.. Atypical / Dysplastic Nevus = Clark's Nevus

Def. : Acquired compound Nevus whose clinical & Histological definitions are Controversial & Still evolving

- **Etiopath** : ① Idiopathic (Sporadic)
  ② familial (Genetic)
  ③ UVL
- **Types** : (1.) Sporadic < Any Age / 1-10 lesions / Risk of MM : 6%

(2.) Familial < 1st decad / 10-100 lesio / Risk (Cumul (100%)

↓

. was previously named « Dysplastic Nevus Synd » now called Familial Atypical Mole & Melanoma (FAMM) synd

. Criteria For D:

(i). FH of malig. melanoma (of 1st or 2nd degree relative)

(ii). > 50 Nevi (some) of c̄ are clinically atypical.

(iii). Dysplastic Histopath.

. **HP**

[1] odd looking Atypical MCs < Epithelioid (End KCs) / Spindle shaped (Elongated)

Proliferate singly & in Nests at DEJ & dermis (c̄ irregular) c̄ may bridge or join Together

[2] Fibrosis, BVs, Infilt.

بورد "العلاج": المتابعة عن طريق التصوير كل ٣ شهور
if Mg → Excision.

	Common Acq. Nevi (Benign)	Atypical Nevi	Melanoma
Asymmetry	. Mirror Image Symmetry	. Some Asymmetry	. Asymmetrical
Border	. Regular & Well defined	. Irreg. & ill defined (not scalloped or Notched)	. very < irreg. / ill defined (Scalloped or Notched)
Color	. Homogenous regularity. (tan - dark brown or skin colored)	. Some-what haphazard (irregularity of Pigm.) c̄ 2-3 Colors [tan, brown, dark brown] But ⊕ gray, blue, whit	. Haphazard (More Complexity)
Diameter	< 5-6 mm (<5)	3-15 mm (>5)	any but usually > 5mm

Malignant Melanoma
(MM)

Def Neoplasm of Melanocytic origin that begins as prolif. of Atypical MCs at DEJ Then by Time → Invade Dermis & S.C.T → ± Lymphatic & Blood spread.

- **Age** :
  - usually > 60 Ys.
  - rare in prepubertals
  - in children usually arise <
    - on Top of Giant or Cong Atypical Nevi (Acq. MM)
    - Transplacental Spread from the affected mother (Cong. MM)

- **incid** :
  - highest rate in < استراليا / نيوزيلندا (30-37 / 100 000)
  - Mortality : 75% of deaths from Cancer is d.t MM
  - في أمريكا بيموت واحد كل ساعة تقريبا في سنة (٢٠١٢) حالة ٩١٨٠

- **Risk factors** :
  1. Fair Complexion (sKin I & II)
  2. Chr. UVL Exposure
  3. precursor Nevi (pre Mg) <
     - Dysplastic Nev. (FAMM)
     - Numerous Atypical Nevi (>5)
     - Giant Nevi
  4. Past Hx or Family Hx of MM
  5. Genetic Mutations. (Gened - وراثية)

70% of MM develop on Top of NL SKIN

NB
- Small-medium sized Cong. Nevi $\xrightarrow{1\%}$ MM
- Giant bathing Trunk $\xrightarrow{5-10\%}$ MM

MM Vs Ear Eye

- other organs Can be affected by MM (sites of MCs
  - Orbit
  - Oral & Nasal Cavity
  - Meninges
  - Vulvae
  - Vagina
  - urethra.
  - [Eye
  - [Ear

Types

④ Main ClinicoPathological Types + others (HL)

In situ Melanoma
(represent Early Radial growth phase) (C/P) Patch

Invasive Melanoma
(represent Late Vertical Growth phase) (C/P: Nodule)

- Lentigo Maligna (LM) $\xrightarrow[(5-20\%)]{\simeq \text{ys}}$ • LM Melanoma
- Acral lentiginous Melanoma (ALM) $\xrightarrow{6-12\text{m.}}$ • Invasive (ALM)
- Superfacial spreading " (SSM) $\xrightarrow{\text{"}}$ • Invasive (SSM)

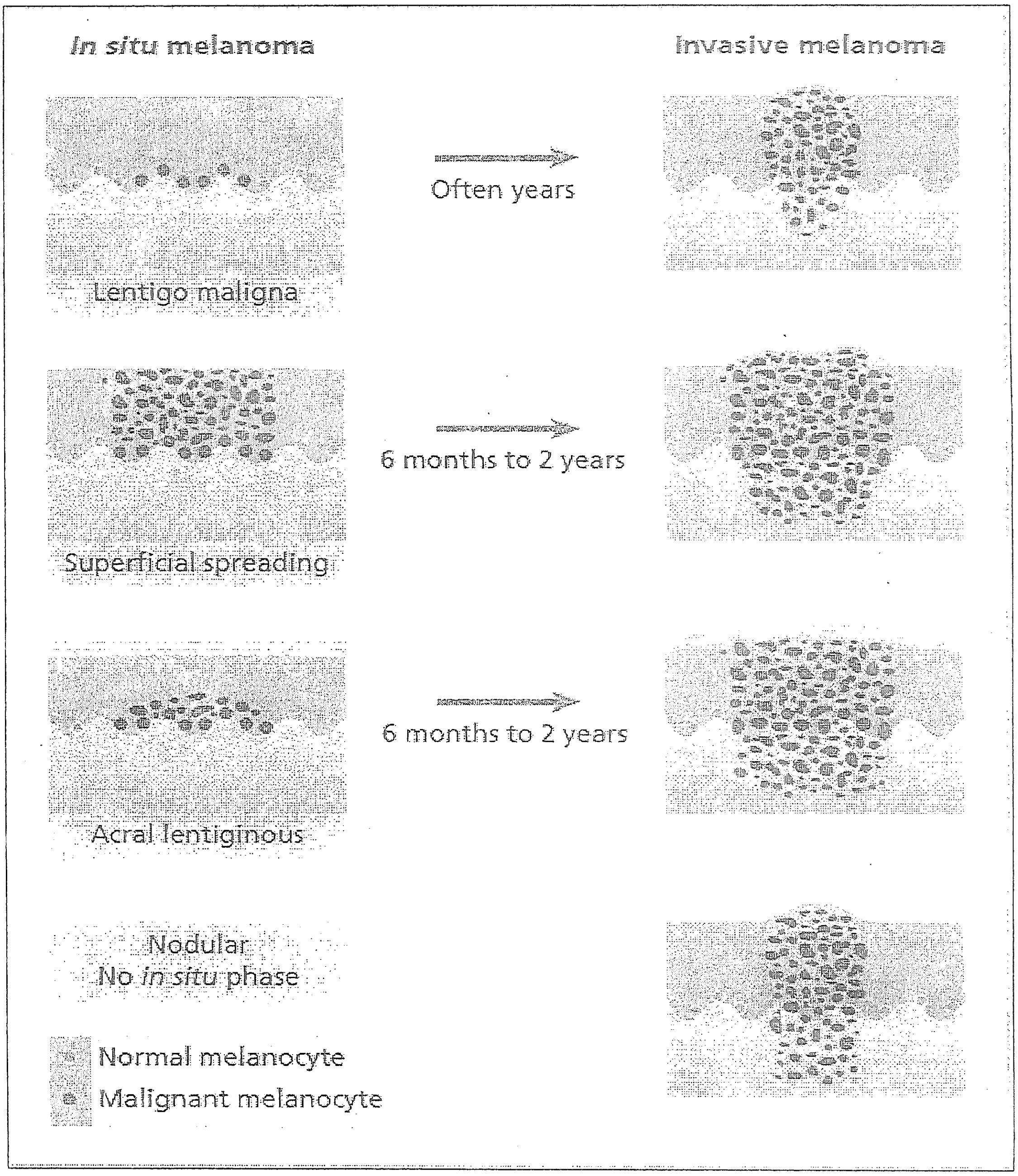
- Nodular Melanoma
  (No Insitu radial growth phase, starts as Invasive).

- Other Types: (دراسي)

Incid
Age
Prog.
Site
— للتذكرة (LANS)

Face ←	• L →	LMM	10%	6th – 7th decade	• best
Acral ←	• A →	ALM	5%	7th decade	• Poor
	• N →	Nodular	15%	5 – 6th "	• Poor
♂: upper back ♀: lower leg.	• S →	SSMM	70%	4 – 5th "	• Poor.

- what is the :
  - Commonest type ?? & rarest Type.
  - best prognosis ??



* Histology of the different types of melanoma.

General C/P of MM

Has 2 Clinicopathological Stage,

Early stage or lesion:

- Clinically: Hyperpigmented Macule / Patch That shows ABCDE &/or Glasgow 7-point checklist Criteria.

- Pathologically. Mg prolif. of Melanocytes in Horizontal direct~ at BMZ (insitu) without dermal Invasion [Early radial growth Plage]

Late stage

- Clinically: Pigmented Nodule (± Non-Pigmented)

- Pathologically: Derma Invasion by Mg. Melanocytes [late Vertical growth phase].

MM usually asympt.: but ± itchy or Tender (e.g. ALM)

The ABCDE of melanoma

A	Asymmetry (2 halves of the lesions are not Symm.) مش زي المرايا
B	Border irregularity (edge: ragged, Notched or Blurred)
C	Colour variation (not uniform; ± أصفر - بني - أحمر - أبيض - أحمر - أزرق)
D	Diameter over 6 mm
E	Evolving. Dramatic Changes in Size & Shape.

Glasgow 7-point checklist

Major features	Minor features
▪ Change in size ▪ Irregular shape ▪ Variable colour	▪ Diameter >7mm. ▪ Inflammation ▪ Oozing ▪ Change in sensation

SSC

Discussion of Each Type

lentigenes → ABCDs change → called lentigo Maligna (insitu MM) → LMM (Invasive).

- **LMM**
  - Incid, Age; as before.
  - Site: • Face sp. cheeks & ears (skin around HF).
    - on Top of Sundamage skin (on Top of Lentigenes)
  - مهم → progression to invasive MM ≃ 5% (Macule → Nodule)
  - C/P (كاسبق) — Early Macular radial growth phase (ē ABCD Glasgow..) / late Nodular vertical " "
  - Varieties: Desmoplastic - Neurotropic - Myxoid

- **ALM**:
  - Incid: Commonest Type in Blacks 50% (10% in whites) rarest Type in
  - Age: —
  - Site: Acral → Palms / Soles (on digits & w.t bearing Heels) → Tender plantar Nodule → Biopsy / Nails (Bed & periungual) → Melanonychia ē +ve Hutchinson sign
    - Acral → "glaberous skin"
  - C/P: كاسبق

- **Nodular M**:
  - Starts as Nodular; radial growth stage (No Macular radial growth phase)
  - Incid, age, site (any) → as before.
  - C/P Varieties:
    - Classical lesion (Pigmented Nodule)
    - Ulcerated "
    - Amelanotic
      - Non Pigmented Nodule (DD ← BCC / PG / Poroma)
      - the Classical lesion in Albinics.

- **SMM**: → كاسبق

- Other Variants of MM

(1) ocular MM : ē Nevus of Ota

(2) Mucosal : mouth, Nasopharynx, Larynx, Vagina & Anus.

(3) Nevoid Melanoma. No epid. involvement.

(4) HP Variants:
  - Desmoplastic → fibrous stroma
  - Neurotropic → perineural invasion → Pain
  - Myxoid → Myxoid Stroma.

(5) Animal type: ē Hairs لشبه موع بيجي

(6) Spitzoid

(7) Blue

- Hutchinson Sign: Subungual Melanoma with extension of Pigmentation To Lat & proximal Nail folds

شفوي

- Pseudo Hutchinson sign : نفس التعريف ~~بس~~ مش بيحصل مع Melanoma [illegible] Benign Condition.

- Hutchinson in Dermatology ??

سؤال أول

Diagnosis of MM.

For
- Melanoma
- L.N
- Metast.

① Clinical
  - ABCDE
  - Glasgow - 7 Point Check list.

②. Dermoscopy

③. HP & Immunohistochemistry

4. SLNB (Sentinel L.N Biopsy)

5. Metastatic work up.

6. Staging of MM

HP

ص.٣ ① **LMM**

- Junctional prolif. of Atypical (Mg) spindle shapped MCs → dermal Nests.
- Adnexal involvement
- Solar Elastosis] [illegible]
- Lymphocytic infilt.]
- little Pagetoid scatters.

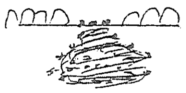
② **ALM**: → Epidermis show: as LMM +

- Hyperplastic
- Pagetoid scatter: Atypical MCs present singly (more common) or in an irregular shapped Nests at all levels of Epid.

No/little Pagetoid < LMM, ALM

- +ve Pagetoid → SMM

③ **Nodular M**: (No radial growth)



, dermal Invasion that connect immediately ē overlying Epid ē No morphologic Abnormality in adjacent epid. on either side of ! Nodule.

④. **Superfacial spreading**.. (Pagetoid Melanoma):

Buckshot pattern. [illegible]

- dermal Nests ē Atypical cells in ! Suprabasal layer of epid. (singly or in clumbs) → simulating EMPD.

Nerve) [illegible]
→ Severe! pain.

⑤ **Desmoplastic, Neurotropic & Myxoid**: 3 Variants of LMM describing the Stroma surrounding the Nests.

⑥ **Nevoid (Small cell Melanoma)**: No epid. Affects ē dermal Invasion by Nevoid cells.

Horses. ← [illegible] ⑦ **Animal Type**: Blue-black Nodule ē sheets of Atypical spindle cells & Heavy dermal Melanin.

لازم تقرير الباثولوجي يجي

عامل تعليق على هذه النقاط

- Diagnosis (كاجينر)
- Breslow Thickness (depth)
- Clark's Level of Invasion
- Lympho, vascular or Neural Invasion, ulcerat
- Mitoses
- Margins.

1- Breslow thickness

The Breslow thickness is reported for invasive melanomas. It is measured vertically in millimetres from the top of the granular layer (or base of superficial ulceration) to the deepest point of tumour involvement. It is a strong predictor of outcome; the thicker the melanoma, the more likely it is to metastasise (spread). (5)

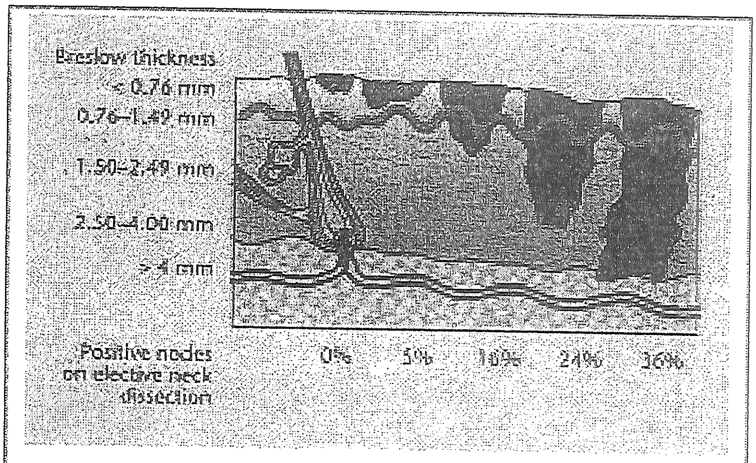
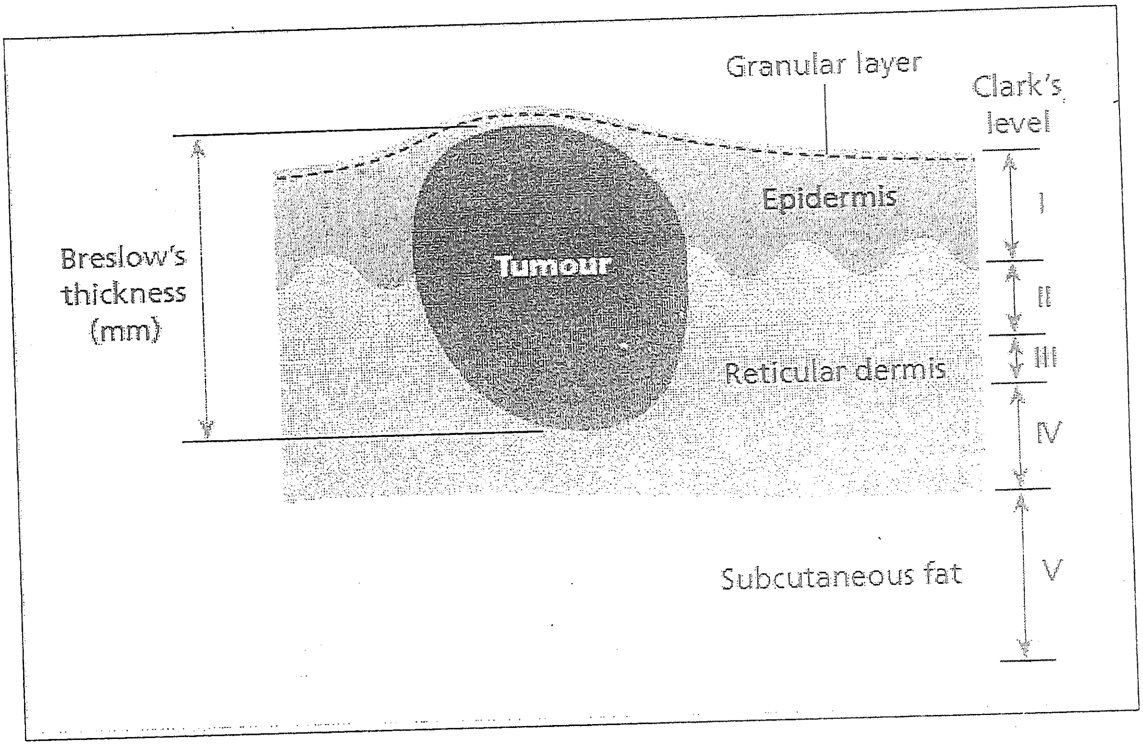


Figure 1a – Breslow Thickness

2- Clark"s level of invasion (5)

Level 1	In situ melanoma
Level 2	Melanoma has invaded papillary dermis
Level 3	Melanoma has filled papillary dermis
Level 4	Melanoma has invaded reticular dermis
Level 5	Melanoma has invaded subcutaneous tissue

The deeper the Clark level, the greater the risk of metastasis (secondary spread). It is useful in predicting outcome in thin tumours, and less useful for thicker ones in comparison to the value of the Breslow thickness.



* Schematic representation of Breslow's and Clark's methods of microstaging malignant melanoma.

- *Immunohistology* (*Immunohistochemistry*)

[illegible]

- *S100* (Ca binding protein):
  - Very sensitive for MCs & Melanoma
  - Most riable for Identifying Spindled M.
  - *NB*: expressed *also* at: neural Cells & Langerhans Cell

- *HMB45/gp100*:
  - Melanosome Specific Glycoprotein gp100.
  - Specific for MCs & Nevus cells.
  - of *limited* benifit ?? false -ve (35%) & Heterogenous staining pattern.

- *Melan-A/MART-1*
- *Tyrosinase*

] - of limited sensitivity

③ SLNB : (ضروري .. اقرأ الـ H)

- done for Staging of regional L.N
- Indication. ① Breslow depth ≥ 1 mm
  - ② presence of:
    - ulcerat
    - Lymphovascular Invasion
    - High Mitoses

- ع ٣ محطات عمل كل منهم Nodal Metastases : (مهم)

N2C:

① dermal / S.C. Lymphatics ē in ≤ 2 Cm from The 1ry Tm → Called « Satellite Metastases »

ii. dermal / SC Lymphatics ē in > 2 Cm from the 1ry Tm but not beyond the region of L.N → called "In Transit Metastases"

iii Regional L.N metastases ĉ may be Macro-Metastases (Causing Clinical Enlargement) or Micro Metast. (LN clinically NL but Histological involve

---

4. Metastatic Work up.

Indication (25) ① Breslow depth / Thickness ≥ 4 mm

② presence of: ulcerati or lymphovascular Inv.

③ +ve SLNB

④ symptomatic patient:
- depth > 4 mm
- Stage > IIC.

- Invs.
  - CXR
  - LDH (أهم) → Marker of Stage IV
  - CT / MRI
  - others : PET, PCR, S100, HMB-45.

Serum = Marker of Metast.

⑤ Staging of MM

٢ طريقة مبسطة وطريقة

3- American Joint Committee on Cancer (AJCC) cutaneous melanoma staging guidelines (2009).

Stage	Characteristics
Stage 0	In situ melanoma
Stage 1	Thin melanoma <2 mm in thickness
Stage 2	Thick melanoma > 2 mm in thickness
Stage 3	Melanoma spread to involve local lymph nodes N
Stage 4	Distant metastases have been detected Mx

الطريقة المفصلة بالطبع لا تحتاج حفظها

Stage	TNM Classification	Histologic/Clinical Features	5-Year Survival Rate, %
0	Tis N0 M0	Intraepithelial/in situ melanoma	100
IA	T1a N0 M0	≤1 mm without ulceration and mitotic rate < 1/mm^2	97
IB	T1b N0 M0	≤1 mm with ulceration or mitotic rate ≥1/mm^2	91-94
	T2a N0 M0	1.01-2 mm without ulceration	
IIA	T2b N0 M0	1.01-2 mm with ulceration	79-82
	T3a N0 M0	2.01-4 mm without ulceration	
IIB	T3b N0 M0	2.01-4 mm with ulceration	68-71
	T4a N0 M0	4 mm without ulceration	
IIC	T4b N0 M0	>4 mm with ulceration	53
IIIA	T1-4a N1a M0	Single regional nodal micrometastasis, nonulcerated primary	78
	T1-4a N2a M0	2-3 microscopic positive regional nodes, nonulcerated primary	
IIIB	T1-4b N1a M0	Single regional nodal micrometastasis, ulcerated primary	54-59
	T1-4b N2a M0	2-3 microscopic regional nodes, nonulcerated primary	
	T1-4a N1b M0	Single regional nodal macrometastasis, nonulcerated primary	
	T1-4a N2b M0	2-3 macroscopic regional nodes, no ulceration of primary	
	T1-4a/b N2c M0	In-transit met(s)* and/or satellite lesion(s) without metastatic lymph nodes	
IIIC	T1-4b N2a M0	Single macroscopic regional node, ulcerated primary	40
	T1-4b N2b M0	2-3 macroscopic metastatic regional nodes, ulcerated primary	
	Any T N3 M0	4 or more metastatic nodes, matted nodes/gross extracapsular extension, or in-transit met(s)/satellite lesion(s) and metastatic nodes	
IV	Any T any N M1a	Distant skin, subcutaneous, or nodal mets with normal LDH levels	< 20
	Any T any N M1b	Lung mets with normal LDH	
	Any T any N M1c	All other visceral mets with normal LDH or any distant mets with elevated LDH	

lines of Treatment of MM

(Emed) 2012

(٣ خطوط)

طبعاً ع كل الحالات — Surgical Excision

- only surgical Excision c̄ Safety Margin: For melanoma < 1 mm depth & No ulceratⁿ, Lympho Vasc. Invasion & low mitoses.
- Excision + LND (SLND)
  - For Tms c̄:
    - (i). $\geq$ 1 mm depth
    - (ii) ulceratⁿ, Lympho-Vasc. invasion, Mitotic rate $\geq 1/mm^2$
- Excision + SLND + Adjuvant TH
  - indications
    - Stage IIB, IIC & III
      - 2-4mm
      - >4mm
      - ← Nodal
      - IFN-α 2b (FDA)
    - Stage: III & IV
      - Chemotherapy:
      - Immunotherapy:
        - IFN α2b
        - Ipilimumab
        - GM CSF
        - Vaccines
      - Radiotherapy.
      - Retinoid Therapy.
      - Vitamins.

Recent Treatments

Melanoma Vaccines:

فكرة إنها بتعتمد على تقديم خلايا أو مستقبلات على سطح الـ MM بتحفز نشاط المناعة فتساعد في العلاج

- Certain HLA & Tm. Ass Ag → ++ NK & HI → Kill Melanoma cells.
- little S.E as Compared to Other Adjuvants.

الدكتورة شرحتها بالتفصيل

BRAF Inhibitors:

Vemurafenib (FDA 201

- Melanomas show Mutatⁿ in Certain pro as BRAF & NRAS → So Inhibition of these Mutated Proteins → Treat MM.
- BRAF Genes are Proto-on

1. 1ry Melanoma Ttt

Excision ē Safety Margin depends on Breslow's depth :

دوريا (JAAD)

SURGICAL TREATMENT OF PRIMARY MELANOMA	
Thickness	Excision margins (cm)
In situ	0.5
<1 mm	1.0
1–4 mm	2.0 + SLND
>4 mm	2.0–3.0 + SLND + Adjuvant

2 Ttt of Regional Metast Melanoma

Ⓐ LN dissect

Management of Regional (L-N)

ELND

اختيارى

(Elective L-N dissect)

Excision of Clinically or rad. NL draining L.N

(No improvement in Survival rate & Carry Risk of Complicat → inf. Hematoma Lymphoedem- disturb Imm. agains MM)

NB

فكرة (ELND)

only 20% of pt ē Tm > 1mm ē out evidence of Metast. (Clinically or radiolgid → Show Micro metastasis.

- So Any Tm ≥ 1 mm thickness Do 1ry Tm Excision + Intraoperative SLND (AJCC) also if ulcerat or Invasion.

SLND

(Selective LND or Sentinel LND)

Technitium Soft & ⌢ blue dye is injected ID at Tm. site → intially drain to Specific Node(s) Called Sentinel (1–2 Nodes)

ودا نحزها كلية

Biopsied (SLNB → Biopsy)

+ve Tm. Cells → Complete L-Node dissect (Sentinel or Selective Lymphadenectomy) & Further Staging

-ve Tm. Cells → No further Surgery.

NB

- SLND

. less Traumatic t
ELND (because
20% Show Micro

. Lymphoscintigra
تحقن دوة لها بتودد
drainig L-Ns الـ LN كرد فعل
عال SLN تقريبا.
بد كتير. بتتبع فرد
لقال الى عرفناه استعمال
يا ز Lymphsc.
زيتع استعمال:
Hand-held g
Counter & V
Inspect (
Inspect
(Hot blue SLN)
↓
قطعها :
① H&E
② Immu Histoch (S100 &
③ RT-PCR

What happens at follow-up?

The main purpose of follow-up is to detect recurrences early but it also offers an opportunity to diagnose a new primary melanoma at the first possible opportunity. A second invasive melanoma occurs in 5-10% patients; an unrelated melanoma in situ affects in more than 20% of melanoma patients. The Australian and New Zealand Guidelines for the Management of Melanoma (2008) make the following recommendations for follow-up for patients with invasive melanoma.

- Self skin examination
- Regular routine skin checks by patient's preferred health professional
- Follow-up intervals are preferably six-monthly for five years for patients with stage 1 disease, three-monthly or four-monthly for five years for patients with stage 2 or 3 disease, and yearly thereafter for all patients.
- Individual patient's needs should be considered before appropriate follow-up is offered
- Provide education and support to help patient adjust to their illness

The follow-up appointments may be undertaken by the patient's general practitioner or specialist or they may be shared.

Follow-up appointments may include:

- A check of the scar where the primary melanoma was removed
- A feel for the regional lymph nodes
- A general skin examination
- A full physical examination
- In those with many moles or atypical moles, baseline whole body imaging and sequential macro and dermoscopic images of melanocytic lesions of concern (mole mapping)

In those with more advanced primary disease, follow-up may include:

- Blood tests, including LDH
- Imaging: ultrasound, X-ray, CT, MRI and/or PET scan.

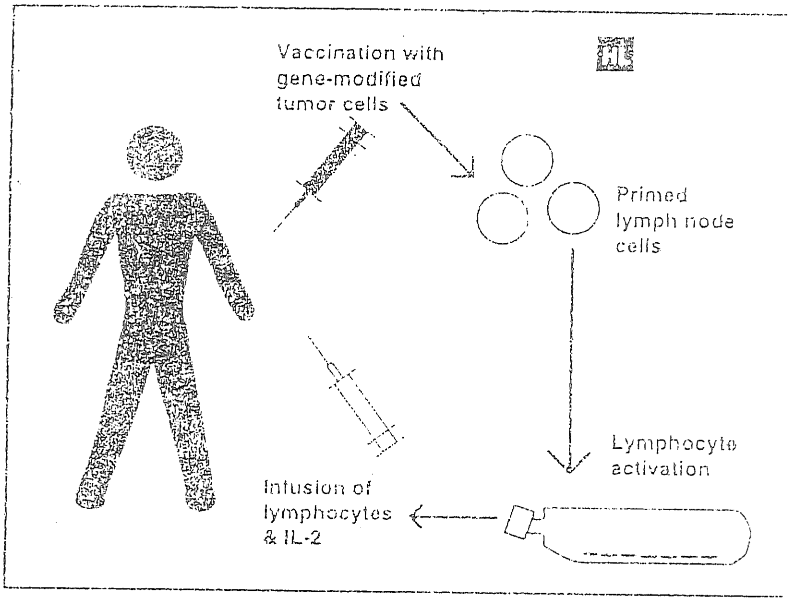
Tests are not typically worthwhile for stage 1/2 melanoma patients unless there are signs or symptoms of disease recurrence or metastasis. And no tests are thought necessary for healthy patients who have remained well for 5 years or longer after removal of their melanoma, whatever stage.

What is the outlook?

Melanoma in situ is not dangerous; it only becomes potentially life threatening if an invasive melanoma develops within it. The rates of melanoma in situ are not reported by cancer registries. The risk of spread and ultimate death from invasive melanoma depends on several factors, but the main one is the measured thickness of the melanoma at the time it was surgically removed.

The Melanoma Guidelines report that metastases are rare for melanomas <0.75mm and the risk for tumours 0.75–1 mm thick is about 5%. The risk steadily increases with thickness so that melanomas >4 mm have a risk of metastasis of about 40%.

New Zealand statistics gathered by the Cancer Registry between 1994 and 2004 revealed 15,839 invasive melanomas. Of these, 52% were under 0.75 mm in thickness, 22% were between 0.76 and 1.49 mm, 15% were between 1.5 and 3 mm in thickness and 11% were more than 3 mm in thickness. Thicker tumours were slightly more likely to be diagnosed in males, and more likely in older people than younger ones.


Vaccination with gene-modified tumor cells
Primed lymph node cells
Lymphocyte activation
Infusion of lymphocytes & IL-2

(NB) Limb perfusion:

- Circulat' of affected limb (is) isolated → Blood slowly heated → Reinfused to the limb again ē high doses of "Melphan| ē or ē out $TNF\alpha$ or $IFN\gamma$.
- when the limb Circ. is isolated from the remaining Systemic Circ. → Much higher doses of therapeutic agents can be administred without marked Systemic

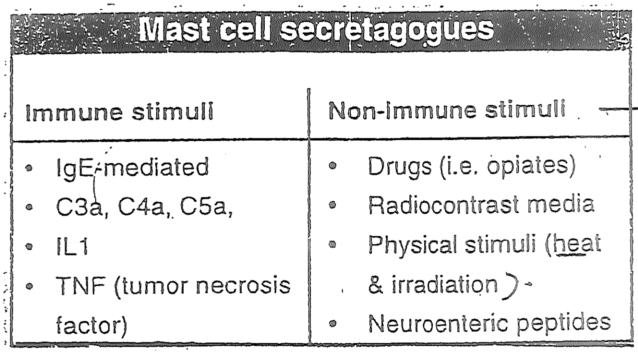
2. Types of Mast Cells: → (3) < C.T / Mucosal

Type	Type of Enzyme	
1. T Type	Tryptase	. Mucosa of < GIT / RT
2. C Type	Chymase	. Skin & L.N
3. TC Type	Tryptase & Chymase	. Skin & GIT (sub-mucosa)

(SL)

(ST)

3. Mast Cells Stimuli (Secretagogues):



Mast cell secretagogues

Immune stimuli	Non-immune stimuli
• IgE-mediated • C3a, C4a, C5a, • IL1 • TNF (tumor necrosis factor)	• Drugs (i.e. opiates) • Radiocontrast media • Physical stimuli (heat & irradiation) • Neuroenteric peptides

Non-immune stimuli → يعني direct Histamine Liberators ??

. Aspirin
. Strawberry
. Vancomycin
. Cs

4. Mast Cells Mediators:

preformed mediators (granules derived)
. Histamin
. Heparin
. Chemotactic Factors < Ⓔ Ⓝ
. Tryptase
. Chymase.

. Serotonin
. Serin.

Newly Formed Mediators (membrane derived) → (eicosanoids)
. PAF
. PGD2
. LTC4
. LTD4
. LTE4
. Cytokines:
. IL4, 5, 6, 8
. TNF-α
. SCF.

NB Mast Cells Secretions → Mediators / Cytokines

. Tryptase & Chymase: + C3 < C3a → ++ Mast Cells / C3b → ++ alternative C. pathway

. Chymase: ++ Mast Cell degran.

5. Hislamin Receptors: 4 Types.

Smoothms → BVs ↓ Relaxat; Bronchi ↓ Contr.

Receptor Type	Major Tissue Locations	Major Biologic Effects
H_1	smooth muscle, endothelial cells Bron Cho Contrl CF, CNS	acute allergic responses → VD & permeability
H_2	gastric parietal cells Smooth ms.	secretion of gastric acid
H_3	central nervous system ↓ NE, ACh, Seroton., presynaptic autoRs → ↓Hist.	modulating neurotransmission
H_4	mast cells, eosinophils, T cells, dentritic cells	regulating immune responses

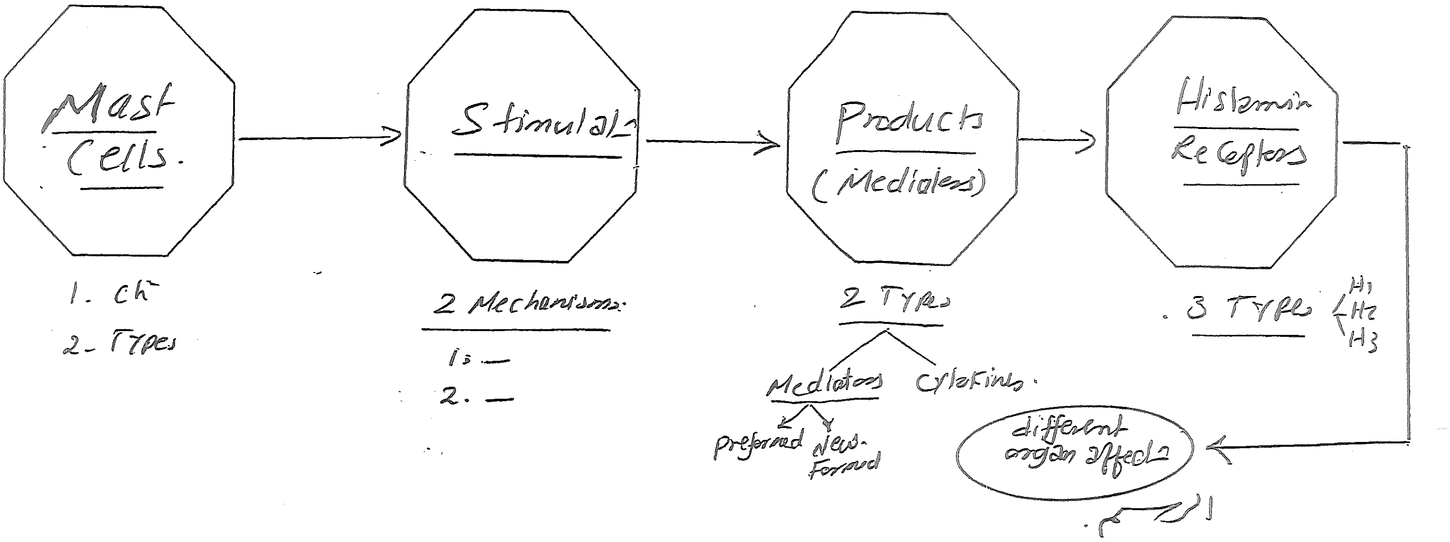
NB Effects of release of Mediators & cytokines: (للتفصيل محاضرة)

باختصار

1. IL4 → ++ B Cells → ↑ IgE
2. IL5 → ++ Eosinophils
3. IL6 → · ↑ IgE
   · ++ TC growth & maturat.
4. IL8 → ++ Neutrophils chemotaxis.
5. TNF-α → ++ All:
   - Neut.
   - Eos
   - Fibroblast
   - Phago-cytosis.

· Blood → Agranulated (monocyte like)
· Skin → granulated.
الفرق بين [illegible]
Blood & Skin.
Mast Cells ??.

(ملخص المقدمة)



الرسم

Mast cell diseases

① Cut. immediate hypersensitivity React., urticaria (IgE)

② AD

③ Allergic CD

④ B.P

⑤ PS: ± develop d.t mast cell mediated vascular alterat.

⑥ PRV → Mast cell → PG → itching

⑦ Fibrotic diseases ← Scleroderma, GVHD, PCT

Host T cells → Lymphokines act as mast cell then mast cell → ++ fibrosis e IL

(a) UVR → ++ Complement → Anaphylatoxins

(b) then Histamine → Released

- (a) ++ Fibroblast mitogenesis
- (b) Collagen synth.

⑧ NF *

Hyper-trophic → ⑨ Scar & Keloid

⑩ wound healing:

1. ++ Collagen synth
2. ++ Vascular permeab.
3. Angiogenesis

⑪ Mastocytosis.

⑫ Necrotizing Vasculitis:

مهم جداً

MastoCytosis

updated 2017

. **Def:** disorder ch. By Mast Cell prolif. & Accumulat. within many organs, Most Commonly the skin.

Etiopathogenesis: . Most Cells Express Cell receptors called : c-Kit (CD117) receptors ⓦ are Rs for stem cell fact (SCF, its Ligand) w is important for Mast Cell prolif

مهم جداً

. Mutat. in c-KIT receptors → (uncontrolled) Stimul of receptors → prolif. & Accumulat. in various tiss

. Inhibiting Tyrosine Kinase receptor ē Imatinib may Treat mastocytosis.

Classificat. of MastoCytosis

↓

3 Classifications:

A. WHO Classificat.: (2001)

Cut. Mastocytosis (5)

- Commonest in children ← . urticaria pigmentosa
- Commonest in Adult. ← . Maculopapular
- Rare Types →
  - . Diffuse Cut.
  - . TMEP
  - . MastoCytoma.
  - . Erythrodermic

شفهي

Cut
Systemic ←
Mast Cell leuk
" " Sarcoma
ExtraCut.

Systemic mastocytosis

- . Indolent
- . Aggressive

- . Mast cell leukemi
- . Mast cell Sarcoma

- . Ass. with clonal Hematological non Mast cell lineage dis. (AHNMD)
- . Extra Cut. mastocytoma.

- **Age**: 2 peaks:

(75%) Infancy & Early-Childhood

Fate ↓
- 50% → resolut-
- 40% → reduct-
- 10% → persist.

at puberty

Adulthood (25%)
(30-50 ys)
↓
usually persistent

75% of Mastocytosis Cases occurs at infancy or Early Childhood

- **Sex**: M = F.

C/P of Mastocytosis

A Symptoms of Mastocytosis:

① There may be: (more in Adult type)
- pruritus
- Flushing
- Abd. pain
- diarrhoea
- Palpitat-
- dizziness.
- Syncope
- Shock.

→ all are physiological Effects of Histamine & mast cell mediators release.

② If there are: Fever, wt loss, malaise, boneache, Epigastric distress & Cognetive disorganizat- $\xrightarrow{\text{indicating}}$ Extracut. dis.

- Symptoms may be ppt by: –
  1. Excercise,
  2. Heat
  3. local Trauma
  4. Alcohol
  - Drugs:
    - Alcohol
    - Salicylates
    - NSAIDs
    - Narcotics
    - systemic anaesth.

B Cut. lesions of Mastocytosis:

الترتيب على حسب الأكثر

Childhood Mastocytosis (< 15 Ys)

1. Generalized (60-90%) → Maculopapular or UP
2. localized (15-20%) → Solitary Mastocytoma. سؤال
3. Diffuse Cut.

Adulthood (> 15 Ys)

1. Generalized Maculopapular ← Commonest
2. TMEP
3. Diffuse Cut.

A. Childhood Mastocytosis:

سؤال امتحان ! 1. Urticaria Pigmentosa (UP) (Childhood generalized Maculopap. Mastocytosis)

- inCid: Commonest Type affecting the children (60-90%)
- onset: Infancy (1st year)
- lesion: Maculopapular:
  - Multiple, generalized, small reddish-brown
  - usually on Trunk but may affect Head & Neck
  - on Rubbing → urticaria (Darier's Sign) $\xrightarrow[\text{by}]{\text{Followed}}$ refractory period of (2-3 ds). ←

شفوي

- Varieties:
  1. Nodular
  2. Vesicular
  3. Bullous Up. → bullae + UP lesion.
  4. Xanthlasmoid UP → Pale-yellow lesions!!

الفرق بين

Bullous UP

&

Bullous Mastocytosis

??

- **Fate:**
  - 50% → resolve at puberty
  - 40% → ↓↓ ~ ~
  - 10% → persist.

2 Localized Mastocytosis → "Solitary Mastocytoma"

- Incid: 15-20% of mastocytosis cases in children (2nd most common).
- onset: infancy or birth
- lesion: → Solitary Nodule or plaque. (± 2-3 Nodules.)
  - Yellow-tan
  - usually on wrist → "dorsal Hand," but may be at Trunk & Neck.
  - Rubbing → +ve Darier sign & may be flushing or even shock
- involut^n: → ≃ 10 y.

3. Diffuse Cut. Mastocytosis: (Erythrodermic or xanthlasmoid Mastocytosis)

- onset: infancy.
- lesion: skin ch. By: (3) -
  - Hyperpigm: → generalized, brownish-orange discolorat^n.
  - Infiltrat^n: → doughy or boggy sensat^n.
  - Lichenificat^n & ± "diffuse blistering".
- varieties: → diffuse cut. blistering may occur so called « Bullous Mastocytosis ».

مراجع

ملخص

All infancy

(1) UP: - reddish-brown macules on Trunk → +ve Darier
- varieties Fate:

(2) Solitary Mast: reddish brown (1-3) Nodule at dorsal wrist → +ve Darier
- onset: ✓
- resolve at: ✓

(3) Diffuse Cut:
- Infilt
- Hyperpigm
- Lichenifical
- Bullous.

B. Adulthood Mastocytosis:

(30-50y)

الفرق عن الأطفال
- Hyperpigm.
- Telangiect
- -ve Darier
- Persist.

1. **Generalized** → Maculopapular Mastocytosis.

Darier Sign less Common

- incid: Commonest Type in adults.
- lesion: reddish-brown macules & papules usually on Trunk & proximal Extremities. ⓦ may show → Hyperpigm. & Telangiectasia.
- Fate: → usually persistent.

كلهم عكس بعض
[illegible]
[illegible]

"Paucicellular Mastocytosis" → 2. **Telangiectasia Macularis Eruptiva Perstans: (TMEP)**

Darier Sign: barely detectable.

- incid: 2nd Commonest Type in adults.
- lesion: ~بالمس~ Macules & Patches with Telangiectasia & non significant Hyperpigm.
- Fate: resistant & persistent.

3. **Diffuse Cut.** → as before but appears on adulthood.

	Childhood Mastocytosis	Adulthood Mastocytosis
Incid:	Most Common (75%)	less Common
lesion:	Commonest Types: ① UP ② Mastocytoma.	Commonest types: ① Generalized Maculopapular ② TMEP.
Darier Sign:	usually +ve	usually: -ve.
Systemic manifs & affect:	less Common	Most Common.
Fate	UP → < Puberty (50%) Mastocytoma at 10y.	Persistent.

● Histopathology of Cut. Mastocytosis.

إحتياطات أخذ العينة في 3 حاجة:

① Inject local anaesth.

But < without epinephrin &
around the lesion

② avoid Trauma or Crushing of the specimen.

all will → Mast Cell degranul. & -ve results

③ تحفظ في محلول ملح ليس في فورمالين

④ إصبغها < Giemsa or TB (Leder) to detect mast cell granules.

Leder stain
X تكتشف
intact mast cell grans.

الأحدث Monoclonal antibodies against < Tryptase or CD117

أدق طريقة (detect abnl mast cells) sp. in adult type that contain few mast cell.

Results:

at papillary dermis

- UP → Mast Cell ch.BY:
  - T.Blue → purple → · Metachromatic grs
  - · Nuclei are rounded with surrounding وافر ample Cytoplasm → Fried Egg appearance.
- TMEP → Mast Cells are brick or spindle shapped.
- Nodular UP. → dense aggregate of Mast Cells may affect entire dermis → S.C.T.

- Diffuse Mastocytosis: dense, band like Subepid; Mast Cell infilt.
- Bullous Mastocytosis: Subepid. bullae.

· Lab. Inv. For Systemic Mastocytosis

① Serum Tryptase

③ BMA: if { pancytop. / ↑ Tryptase / HSM

② Urinary: Histamine, N-Methyl histamine, N-methyl Imidazole acetal, PGD2

Lab Inv.

- **mild Cut**
  - ↓ No lab abnormalities
- **Sever Cut**
  - (i). **Urine**
    - Histamine
    - N-methyl histamine ⎤
    - N. Methyl-Imidazole acetate ⎦ → Sens. & specific
    - **PGD2** (غير مشهور)
- **Systemic**
  - ↓ as Sever Cut +
  - 1. **Tryptase** (Serum)
    - [لكنه ممكن يعلى في مرضى [illegible]
    - سابقة مع Insect bite |
  - 2. **CBC**
    - anemia
    - ↑ WBC
    - Eos.
  - 3. **BMA**
    - pancyt.
    - ↑ Tryptase
    - HSM

Systemic Mastocytosis

WHO

- Cut. mastocytosis
- Systemic " ——— Indolent / Aggressive / Ass. ē Clonal-Hematological non-mast Cell lineage dis (SM-AHNMD)
- Mast Cell Leukemia
- Mast Cell Sarcoma
- Extra Cut. Mastocytoma

WHO Criteria of Systemic Mastocytosis

- **Major**: Mast Cell infilt. → Multifocal / > 15 cells in aggregates / BM &/or extracut. affect
- **Minor**:
  - > 25% of These ↑ mast cells are → Spindle or Atypical
  - Tryptase > 20 ng/ml
  - A Codon 816 KIT Mutation
  - Aberrant expression of CD25 &/or CD2

- **For diagnosis**

  1 J + 1 M or 3 minor.

NB

. **Darier sign**

① +ve in 2 dis ⟨ mastocytosis / Leukemia Cuti

② **-ve in Adulthood mastocytosis ??**

d.t low concentrat° of infilterating mast cells e.g

- . Solitary mastocytoma : 140 fold
- . Urticaria pigmentosa : 40 "
- . Adult mastocytosis : 8 "

} The NL skin.

So ⟨ TMEP / Generalized / Adult mast. Called ((Pauci-Cellular Mastocytosis))

Treatment

(Symptomatic ; No Cure)

① **Reassurance** : in childhood Type

② **Avoid mast cell degranulators**

"Anaphylaxis" ← ag ↓

- . Alcohol, Aspirin, NSAIDs, Narcotics & Systemic (Not local) Anaesthesia
- . Heat, Frict°

③ **local** :

- . Cs : Potent & Superpotent ; ± under occlusion
- . IL Cs

④ **oral** :

- . Antihistamines (H1 & H2 blocker)
- . mast cell stabilizers
- . Systemic Cs
- . PUVA.

⑤ **Aggressive (Systemic mastocytosis**

- . Imatinib methylate or
- . IFN-α 2b.